REMARKS

Applicants acknowledge receipt of the Office Action mailed February 18, 2009. Applicants have carefully considered all rejections raised by the Examiner and respond hereto in detail.

Rejection of Claims 1 and 2 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1 and 2 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* (Chirality, 12:26-29, 2000) in view of Makarova (Russian Journal of General Chemistry, 71(7):1126-1129, 2001), Gribble *et al.* (Org. Prep. Proc. Int, v. 17, pp. 317-384, 1985), and March (March's Advanced Organic Chemistry, 5th ed., 2001, Wiley, pp. 970-1298).

However, the presently claimed invention is nonobvious over the cited combination. As will be explained below, the presence of carboxylic acid is not a routine element for tuning the presently claimed method. Rather, the presence of carboxylic acid is a critical distinction of the presently claimed invention, which distinguishes the present invention from the prior art. Moreover, it is clear from the Gribble reference and the Bartoli reference cited by the Examiner on the PTO-892 Form that it is far more difficult to carry out the reduction reactions and far less predictable than asserted in the Office Action. In spite of these difficulties, the present invention achieves an extremely remarkable effect of producing an N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine in a high yield by using a specific reaction raw material under a specific condition, such as by using a (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine in the presence of a carboxylic acid.

The Examiner relies on the March reference for a teaching that carrying out reduction in the presence of a carboxylic acid can be used to "tune reactivity." Applicants are not certain exactly where in the March reference such a teaching can be found, and respectively request that the Examiner point out this teaching. Nevertheless, even if March does teach that carboxylic acids can be used in certain reduction reactions, March certainly does not provide any teaching of the criticality of the carboxylic acid in the context of the presently claimed method.

Applicants are providing herewith a Declaration of Kenji Kogami under 37 C.F.R. § 1.132. The Declaration shows that, in the presence of a carboxylic acid, the reduction reaction of the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine proceeds significantly, enabling the production of N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine at a high yield. In contrast,

when the reaction is carried out without the presence of the carboxylic acid, the reaction virtually fails to proceed at all. In view of the Declaration, it is clear that this distinction from the prior art is a critical distinction, which could not have been predicted by one having ordinary skill in the art.

The Declaration makes clear that it is not necessarily predictable that a reduction reaction of any given compound can proceed in the absence of the proper conditions, such as the carboxylic acid required for the present reaction. Two of the references of record in the present application further support this contention of Applicants. The first of these references is the Gribble reference cited by the Examiner.

The Gribble reference teaches that when a β-enamino ketone having a phenyl group is reduced in the presence of a carboxylic acid, the oxo group and double bond are not reduced. Rather, the amino group is eliminated (See page 327, Table 3 last entry). This elimination of the amino group is observed for a β-enamino ketone having a pheny, isopropypyl or cyclohexyl group. This supports Applicants' argument that the conditions for reduction are not necessarily predictable.

Moreover, the Bartoli *et al.* (J. Chem. Soc. Perkin Trans. 1, 537-54(1994)) reference cited on the PTO-892 Form also shows the difficulty and lack of predictability in carrying out reduction reactions on specific compounds. It is generally known that the selective reduction of the oxo group and double bond of β-enamino ketones, to which the reaction raw material of the present invention, *i.e.*, the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine belongs, is difficult. As an example, Bartoli discloses that the reduction of β-enamino ketones takes place with difficulty, and that these compounds can be reduced in low yields to γ-amino alcohols (see page 537, left column). Bartoli *et al.* further teaches:

> (w)e also tried new efficient and powerful reducing systems such as $NaBH_4$ in the presence of acids ($CeCl_3$,[14] $ZnCl_2$,[15], $FeCl_3$,[16] H_2SO_4,[17] etc.) but no appreciable results have been obtained. *See* page 537, right column, line 3 from the bottom to page 538, left column, line 1.

Thus, Bartoli et al. further supports Applicants' argument that one of ordinary skill in the art cannot predict the conditions required for reduction of a given a compound. In view of these difficulties, the results reported in the Declaration regarding the ability of carboxylic acid to permit the reduction reaction to proceed while no appreciable reaction occurs in the absence of carboxylic acid are truly remarkable and unexpected. These unexpected results evidence the

nonobviousness of the presently claimed invention even in the presence of a *prima facie* showing of obviousness.

However, a *prima facie* showing of obviousness cannot be sustained on the basis of the presently cited references. In particular, Gribble directly teaches away from the present invention in which a β-enamino ketone (*e.g.* (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine) is reduced to provide an γ-amino alcohol (*e.g.* N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine) in the presence of carboxylic acids. As discussed above, the Gribble reference teaches that when a β-enamino ketone having a phenyl group is reduced in the presence of a carboxylic acid, the oxo group and double bond are not reduced. Thus, the Gribble reference would lead one having ordinary skill in the art not to include the recited carboxylic acid. In direct contradiction to the teaching of Gribble, the Applicants have discovered that the carboxylic acid is critical for the recited reaction to occur. MPEP 2141.02 specifically notes that "a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." In view of the Gribble references teaching away from the invention rather than toward it, the cited combination of references cannot support a *prima facie* showing of obviousness.

Additionally, the N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one of Makarova is rather a particular example, and its reduction is attributed to the unique reactivity of the adamantyl group, whose structure and chemical characteristics are completely different from those of thienyl group. The (*Z*)-N-monoalkyl-3-oxo-3- (2-thienyl)propenamine, *i.e.*, the raw material of the present disclosure, is different from the N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-l-en-3-one of Makarova, and its reduction reaction proceeds negligibly in the absence of a carboxylic acid.

Accordingly, even a person skilled in the art cannot predict that the use of a carboxylic acid allows the reduction of the oxo group and double bond of the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine to significantly proceed, ensuring the production of N-monoalkyl-3-hydroxy-3-{2-thienyl)propanamine in a high yield, from the teachings of Liu *et al.*, Makarova, Gribble *et al.*, and March.

Moreover, combining the enzymatic process of Liu *et al.* with the sodium borohydride reduction of Makarova would render the enzymatic resolution of Liu *et al.* unsatisfactory for its intended purpose. Further, the combination of the Finkelstein reaction of Liu *et al.* or alkylation

of Liu *et al.* with the sodium borohydride reduction of Makarova would also render these steps unsatisfactory for their intended purpose. Regardless of the motivation that Liu provides, the intended purpose of Liu is to provide a "Chemo-Enzymatic Synthesis of the Antidepressant Duloxetine and Its Enantiomer." Thus, the combination of the method of Liu *et al.* with the method of Makarova would render the Liu *et al.* method unsatisfactory for its intended purpose. As set forth in M.P.E.P. 2143.01(V) "if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. Thus, for this additional reason, a proper *prima facie* showing of obviousness cannot be established on the basis of the cited references.

Thus, Applicants submit, that for all of the preceding reasons, no proper *prima facie* showing of obviousness of Claims 1 and 2 can be established on the basis of the cited combination of Liu *et al.* in view of Makarova, Gribble *et al.*, and March. Moreover, even if such a showing had been established, the significant unexpected results produced in the presence of carboxylic acid would rebut any such showing. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 4 and 5 under 35 U.S.C. § 103(a)

The Examiner asserts that Claims 4 and 5 are obvious over Liu *et al.* in view of Makarova. Specifically, the Examiner states as follows:

> (i)n addition, one of ordinary skill in the art would immediately recognize how to modify the reaction to produce the claimed invention based on the teachings of Makarova.

However, as explained above, Makarova merely discloses an N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one, whose structure and chemical characteristics are completely different from those of the (*Z*)-N-monoalkyl-3-oxo-3- (2-thienyl)propenamine. Further, Makarova does not disclose the stereochemistry of the N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one double bond. Thus, Makarova and Liu *et al.* do not teach, alone or in combination, 2-thienyl β-aminovinyl ketones with *Z* stereochemistry. For at least these reasons Claims 4 and 5 are not obvious over Liu *et al.* in view of Makarova. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this reason.

As discussed previously, the reduction of the N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one described in Makarova is a particular case, and is attributed to the unique

reactivity of the adamantyl group. Therefore, if the adamantyl group of the compound is replaced with another group, the reduction reactivity will be completely changed, which is difficult to predict.

Further, as stated above, even when various β-enamino ketones having a substituent other than adamantyl, such as phenyl, are reacted with a reducing agent, almost no reduction reaction is observed, or nitrogen or oxygen is split from the molecule. The difficulty in reducing the double bond and the oxo group of β-enamino ketones is thus known.

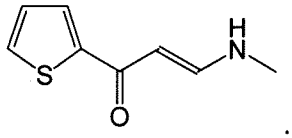
In fact, the reduction of the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine does not effectively proceed in the absence of a carboxylic acid, as discussed in the Declaration of Kenji Kogami provided herewith.

The (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine of the present invention produces the N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine at a high yield when a carboxylic acid is used as a proton source, this allows the reduction reaction to significantly proceed contrary to when a carboxylic acid is not used as a proton source. In other words, the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine acts as an effective reaction raw material for formation of the N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine in the presence of a carboxylic acid.

Accordingly, even a person skilled in the art cannot predict that a β-enamino ketone (e.g. (*Z*)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine) is useful as a starting material for production of a γ-amino alcohol (e.g. N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine), from Makarova which merely teaches a reduction reaction of a β-enamino ketone (e.g. N,N-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-one) without a carboxylic acid. Thus, Liu does not provide motivation to use (*Z*)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine as a starting material based on the teaching of Makarova. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this additional reason.

The Examiner has suggested combing a moiety of the compounds of Liu *et al.* with a moiety of the compounds of Makarova *et al.* in a piecemeal fashion to arrive at the current invention. "It is not proper to dissect claims and reconstruct them in piecemeal fashion by picking and choosing from among the prior art references using the patent as a blueprint. *In re Kamm*, 452 F.2d 1052, 1056-57, 172 USPQ 298, 301-02 (CCPA 1972). Accordingly, Applicants respectfully request withdrawal of the rejection for this additional reason.

The Examiner has maintained the prior rejection of Claims 4 and 5 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova. The Examiner alleges that Claims 4 and 5 read on:



The Examiner's allegation is manifestly incorrect. The Claims do not read on the above structure. The Examiner has misinterpreted the structural differences between *E* and *Z* isomers of the double bond. The Examiner has indicated "(t)he declaration of Takahashi Naoko under 37 CFR 1.132 filed 11/13/08 is insufficient to overcome the rejection of the claims based upon 35 USC 103 as set forth in the last Office action..." The Applicants provided exhaustive detail concerning the differences of E and Z isomers in the Declaration of **Satake Syuzo** of November 13, 2009. There was no declaration of Takahashi Naoko on November 13, 2009. The Applicants respectfully request the Examiner withdrawn this rejection as Claims 4 and 5 do not read on the above *E* isomer. As established in the Declaration, the two isomers have dramatically different properties. As set forth in MPEP 2141.02, "a compound and all its properties are inseparable." (citing *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)). In view of the dramatically different properties of the recited isomer from the isomer in the cited prior art reference, the claims are nonobvious over the cited combination of references.

The Examiner has withdrawn the previous rejection of Claims 4 and 5 under 35 U.S.C. § 103(a) as being obvious over Cassella Farbwerke *et al.* (CA 115:29157), Singh *et al.* (CA 115:29157) and/or Bogdanowicz-Szwed *et al.* (CA 136:118356) alone or in combination. The Applicants thank the Examiner for the withdrawal of the rejection.

Rejection of Claim 6 under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 6 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova *et al.*, Wright *et al.* and Guseninov *et al.*

The Examiner states that the cited art are relevant due to the method of the amination technique. However, Wright *et al.* teaches a hydroxyamination technique of making vinylogous hydroxamic acids not a technique of making *Z*-vinylogous amides. The Examiner states that "the Wright reference does teach the same stereochemistry as the claims." This implies that vinylogous amides and vinylogous hydroxamic acids are structurally the same. This is incorrect.

For example, Wright *et al.* teaches a method of making vinylogous hydroxamic acids from *E*-vinylogous amides. *See* Method B page 4067. Further, the thienyl examples from Wright *et al.* (Table I entries **2oo** and **2qq**), were synthesized by Method B. The first step of Wright *et al.* Method B provides an *E*-vinylogous amide which the Examiner must acknowledge is different than a Z vinylogous amide as disclosed in Claim 6. The *E*-vinylogous amide of Wright *et al.* Method B step 1 is further converted to a vinylogous hydroxamic acid in step 2. Wright *et al.* Method B step 2 does not provide a *Z*-vinylogous amide as disclosed in Claim 6. Methods A-D, disclosed in Wright *et al.*, all are directed to providing vinylogous hydroxamic acids. Additionally, Wright *et al.* does not disclose using a salt form (e.g. sodium salt) of the β-ketoaldehyde to provide a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Thus, any combination of references with Wright *et al.* would not provide a method of synthesizing a *Z*-vinylogous amide (*e.g.* (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine) as disclosed in Claim 6. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this reason.

As discussed in a previous Office Action response, the Example the Examiner has cited in Guseninov *et al.* discloses formation of an α-chloro-β-aminovinyl ketone where the ketone and the amino group have *E* stereochemistry in relation to each other. This is in contrast to the method of Claim 6 which does not include an α-chloro moiety and provides the *Z* isomer of *N*-methyl-3-oxo-3-(2-thienyl)propenamine. *See* Example 1 pages 1-2, Declaration under 37 C.F.R. § 1.132 by Syuzo Satake (November 13, 2009). Additionally, Guseninov *et al.* does not disclose using a salt form (e.g. sodium salt) of the β-ketoaldehyde to provide a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Thus, any combination of references with Guseninov *et al.* would not provide a method of synthesizing a *Z*-vinylogous amide (*e.g.* (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine) as disclosed in Claim 6. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this additional reason.

Additionally, any modification of Guseninov *et al.* with Makarova (or any similar method to that disclosed in Makarova) would render Guseninov *et al.* unsuitable for it's intended purpose which is formation of an α-chloro-β-aminovinyl ketone where the ketone and the amino group have *E* stereochemistry in relation to each other. The M.P.E.P states: "(i)f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d

900, 221 USPQ 1125 (Fed. Cir. 1984). Accordingly, Applicants respectfully request withdrawal of the rejection for at least this additional reason.

Rejection of Claims 7 and 8 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 7 and 8 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova, Wright *et al.*, Guseninov *et al.*, Gribble *et al.* (Org. Prep. Proc. Int, v. 17, pp. 317-384, 1985), March (March's Advanced Orgnanic Chemistry, 5th ed., 2001, Wiley, pp. 970-1298), and Makarova-2 (Russian Journal of Organic Chemistry, Vol. 37, No. 8, pp. 1099-1101, 2001). The Examiner states that "one of ordinary skill in the art has well within their technical grasp to the ability to reformulate reactions using numerous methods available as taught by March and Liu, for example." The Examiner states that Liu is teaching desirability of developing an optimum synthetic route to the drug precursor. This is incorrect. Liu *et al.* discloses their desire to synthesize a drug precursor and their specific method of the synthesis of said precursor. It is unclear how the examiner proposes to combine the teachings of Liu *et al.* with the teachings of March or Makarova-2. The Examiner states that using the motivation of Liu is enough to guarantee a successful synthesis in view of Makarova-2. This is incorrect. Gribble *et al.* and Bartoli *et al.* were motivated to reduce β-enamino ketones, however this motivation did not result in the reduction of β-enamino ketones in the presence of a carboxylic acid. Accordingly, the Applicants respectfully request withdrawn this rejection for at least this reason.

As discussed above, combining the enzymatic process of Liu with the sodium borohydride reduction of Makarova would render the enzymatic resolution of Liu unsatisfactory for its intended purpose. Further, the combination of the Finkelstein reaction of Liu or alkylation of Liu with the sodium borohydride reduction of Makarova would also render these steps unsatisfactory for their intended purpose. Additionally, combining the enzymatic process of Liu with the condensation of Makarova-2 would render the enzymatic resolution of Liu unsatisfactory for its intended purpose. Further, the combination of the Finkelstein reaction of Liu *et al.* or alkylation of Liu *et al.* with the condensation of Makarova-2 would also render these steps unsatisfactory for their intended purpose. Accordingly, the Applicants respectfully request the Examiner withdrawn this rejection for at least this additional reason.

Further, as discussed above, Gribble *et al.* clearly teaches away from reducing a β-enamino ketone to provide γ-amino alcohols in the presence of carboxylic acids. The Bartoli et al. reference further supports the difficulty in obtaining the results achieved by the presently claimed invention. Accordingly, the Applicants respectfully request the Examiner withdrawn this rejection for at least this additional reason.

Moreover, the combination of Liu *et al.*, Makarova, Wright *et al.*, Guseninov *et al.*, Gribble *et al.* March and Makarova-2 do not teach or suggest each element of the claims. For example, the references do not teach the reduction of a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine in the presence of a carboxylic acid. Thus, for at least this additional reason and the reasons set forth in reference to Claim 6, these references would not lead one of skill in the art to the method of Claims 7 and 8. Accordingly, Applicants respectfully request withdrawal of the rejection for at least this additional reason.

Discussion of Obviousness-Type Double Patenting

In the Office Action, the Examiner provisionally rejected Claims 4 and 5 as being objected to under the judicially created doctrine of double patenting as being unpatentable over copending Application No. 11/989,100. In response, Applicants again respectfully request that the issue of obviousness-type double patenting be deferred until such time as either the present application or the co-pending application are in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7/14/09

By: _____

Neil S. Bartfeld, Ph.D.
Registration No. 39,901
Agent of Record
Customer No. 20995
(619) 235-8550

7428715
070809